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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WHALEY, PABLO S	

ART UNIT	PAPER NUMBER
1631	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/644,594	FRUDAKIS ET AL.
	Examiner	Art Unit
	Pablo Whaley	1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 07/10/2007.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1 and 83-115 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1 and 83-115 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 03/26/2007.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

CHANGE OF EXAMINER

It is noted that the Examiner of record has changed. Please address all future responses to Examiner Pablo S. Whaley, USPTO, Art Unit 1631.

REQUEST FOR CONTINUED EXAMINATION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/26/2007 has been entered.

APPLICANT'S ELECTION

Applicant's election with traverse of the combination of SEQ ID Nos: 1, 3, 7, 8, 11, 21, 40, 59, 63, 70, and 331, in the response filed 07/10/2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). However, as the instant claims have been amended to no longer recite specific sequences this election is hereby withdrawn.

CLAIMS UNDER EXAMINATION

An action on the merits of claims 1 and 83-115 follows. Claims 2-82 are cancelled.

INFORMATION DISCLOSURE STATEMENT

The information disclosure statements filed 03/26/2007 has been considered in full.

PRIORITY

Priority to US Provisional Application 60/404,357, filed 8/19/2002 has been acknowledged.

CLAIM REJECTIONS - 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 83-115 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 84, and 91 are rejected for the following reasons. Claims which are directly or indirectly dependent from claim 1 are also included as rejected herein, due to said dependence.

Claim 1, step c): There is lack of antecedent basis for "SNPs hybridizing in step (b)". There is no previous recitation of any step of hybridization. Correction is requested.

Claim 1, step c): It is unclear if "a SNP <u>which may be correlated</u> with but not linked to a gene-linked trait" is intended to be an active method step of correlation or not. Clarification is requested via clearer claim language.

Claim 1, step f): It is unclear as to the metes and bounds of "proportional ancestry" such that an artisan would know what constitutes this limitation, which could be interpreted as mixtures within an individual or within a population, for example. Clarification is requested via clearer claim language.

Claim 84: It is unclear what limitation is intended by "determining an <u>Fst >0.4</u>." Clarification is requested via clearer claim language.

Claim 91 recites "maximizes a cumulative delta value between, and minimizes a difference in cumulative delta value within, each of the one or more pairs of the population." It is unclear whether "each of the one or more pairs" relates to a cumulative delta value between, a cumulative delta value within, or both. Clarification is requested via clearer claim language.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements appear to be: (1) a step directed to "determining the nucleotide occurrences of a first population of SNPs", and (2) determining minor allele frequencies of SNPs, between the step b) "contacting a parental sample" and step c) "selecting SNPs hybridizing in step b)." Clarification is requested.

Claim Rejections - 35 USC § 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 83-115 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

Claim 1 has been amended to recite "contacting a sample comprising nucleic acid molecules of a <u>non-parental</u> individual with the second population of SNPs." In the response filed 07/10/2007, applicant does not point to support for the newly recited limitation, specifically the recitation of samples from "non-parental" individuals. The Examiner has not found support for this limitation and this limitation is not present within the scope of the original claims as filed. As the newly recited limitations are not supported by the originally filed claims or disclosure, the claims are rejected for reciting new matter. This rejection is necessitated by amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 84-86, 90, 92-97, 100, 104, and 105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Parra et al. (Am. J. Physical Antropol., January 2001, Vol. 114, Issue 1, p. 18-29), in view of Ott et al. (HUMAN MUTATION, 2001, Vol. 17, p. 285-288) and Halushka et al. (Nature Genetics, 1999, Vol. 22, p.239-247).

The instant claims are directed to a method of inferring proportional ancestry of at least two ancestral groups of an individual by identification of a population structure comprising steps generally directed to: identifying a first population of SNPs; contacting a parental sample with hybridizing nucleic acids corresponding to said first population of SNPs; selecting SNP hybridizing to generate a new population of SNPs; contacting non-parental samples with the second SNP population; determining the nucleic acid occurrences of the second population of SNPs; and identifying the population structure indicated by the nucleotide occurrences determined for the non-parental individual.

Parra discloses a method for inferring ancestral proportions and admixture in six different populations from different regions [See Abstract]. Parent populations and non-parental populations are discloses [p.19, Subjects and Methods]. A population of ten SNP markers comprising and delta values > 0.4 between one or more populations are identified [Table 1, last column], as in claim 1, step a. Parent samples (i.e. African and European) are contacted with markers using standard PCR genotyping for determining allele frequencies [See p.20, Col. 1 and Table 1, last column], as in claim 1, step b. A combination of SNP markers are selected to obtain an estimate of admixture for a sub-population of six African-American samples (i.e. non-parental samples) [p.21, Col. 1, ¶ 2] comprising three different groups [Fig. 1], as in claim 1, step c. Allele frequencies of the SNP markers are also > 1% [Table 1], as in claim 1, step c. Two of the ten markers are unlinked to any of the remaining loci (FY and AT 3], as in claim 1, step c.

The population structure is then determined using a predetermined confidence interval and infers the proportional ancestry of the non-parental population [p. 21 and Table 2], as in claim 1, steps d-f. Therefore claim 1 is anticipated.

The following dependent claims are also taught by Parra et al: The disclosed populations comprise different African and European groups that are both intracontinental and intercontinental [Table 1, Fig. 1, and p. 22], with delta values > 0.4, as in claims 84-86 and 94-95. Parra discloses steps similar to those of instant claim 1. Parra discloses biogeographical ancestry trait (BGA) [Fig. 1], as in claim 90. Admixture proportions of samples were estimated using the ADMIX program based on maximum likelihood calculations [p.20, Col. 2, ¶2 and ¶3], as in claims 92-93. Proportional ancestry comprising a three-way comparison of sub-populations of African-Americans and the distribution percentage of European alleles within this sub-population [Fig. 1] derived from maximum-likelihood methods [p.25, Col. 2], as in claims 96-97, 100. As SNPs are detected in a subpopulation of non-parental individuals, as set forth above, to determine admixture proportions (i.e. European) and population structure, claims 104 and 105 are also anticipated.

Parra et al. do not specifically teach the selection of a second group of SNPs with minor allele frequencies > 1%, as in claim 1. However, Parra et al. teach fitting genotype frequencies to Hardy-Weinberg proportions and suggest the selection of genetic markers that show homogeneity with Africa and Europe [p.20, Statistical Analysis], which is suggestive of minor allele frequency calculations. Parra et al. do not specifically discloses the BGA comprising East Asian ancestral groups.

Ott et al. teaches a two-stage method for the selection of a subset (i.e. second population) of SNP markers from a larger set of markers with a predetermined significance value [Introduction], as in claim 1. Ott et al. also teaches their method beneficially addresses

the problem of large differences between case and control data sets resulting from disease genes near markers and population structure [Introduction], and applies their method to identify 89 SNPs in heart disease patients [p.237, col. 1].

Halushka et al. teach a method for selecting SNPs informative of hypertension with minor allele frequencies > 1% which are classified by their occurrence among individuals of either African or European descent (population specific) or their presence in both (shared) [Methods] and [Fig. 2]. The frequency spectrum shown [Fig. 2] uses the minor allele frequency (<50%) at each variant site, as in claim 1. SNPs for coding and non-coding regions are also presented [Table 2].

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of Parra to use a two-stage approach for selecting a second population of SNPs with strict adherence to a predetermined significance value, as taught by Ott et al., with minor-allele frequencies > 1%, as taught by Halushka et al., as it is well known that minor allele frequency plays a role in SNP detection, as taught by Halushka above, resulting in the practice of the instantly claimed invention with predictable results. One of ordinary skill in the art would have been motivated to combine the above teachings in order to improve ancestral prediction by reducing the number of genetic data used, as provided by Ott, and to estimate the relationship of individual admixture to disease status (e.g. hypertension), as provided by Halushka.

Claims 87-89, and 110-115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Parra et al. (Am. J. Physical Antropol., January 2001, Vol. 114, Issue 1, p. 18-29), in view of Ott et al. (HUMAN MUTATION, 2001, Vol. 17, p. 285-288) and Halushka et al. (Nature Genetics,

1999, Vol. 22, p.239-247), and further in view of Sorenson et al. (US 2003/0172065; Filed Mar. 29, 2002)

Parra, Ott, and Halushka make obvious a method for inferring ancestral proportions and admixture, as set forth above.

Parra, Ott, and Halushka do not specifically teach the number of SNPs as in claims 87-89, or a photo of a person from whom the known proportional ancestry was determined, as in claims 110-115.

Sorenson discloses a genealogical research and record keeping system for identifying commonalities in haplotypes from biological samples [Abstract]. In particular, Sorenson teaches thousands of known genetic markers and millions of characterized SNPs may be analyzed [0042], [Fig. 4] for identifying a population structure [fig. 4] and [0032], [0046]-[0047] that correlates with markers and a trait, as in claim 87-89. Sorenson also discloses prior art genetic records of human eye, hair and skin color, height and other physical characteristics [0009], and ancestral data stored on microfiche and on a number of other electronic media formats including the internet [0003], which is broadly interpreted as a teaching for digital information and pictures as in claims 110-115.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of Parra, Ott, and Halushka in combination with the records keeping system taught by Sorenson et al., in order automatically correlate genetic information with genealogical information to identify previously unknown biological relationships [Sorenson, 0015], resulting in the practice of the instantly claimed invention with predictable results.

Claims 97-99, 101-103, and 106-109, are rejected under 35 U.S.C. 103(a) as being unpatentable over Parra et al. (Am. J. Physical Antropol., January 2001, Vol. 114, Issue 1, p. 18-29), in view of Ott et al. (HUMAN MUTATION, 2001, Vol. 17, p. 285-288) and Halushka et al. (Nature Genetics, 1999, Vol. 22, p.239-247), and further in view of Kanetsky et al. (*Am. J. Hum. Genet.*, Published 2/6/2002, Vol. 70, p. 770-775), Pritchard et al. (Theoretical Population Biology, 2001, Vol. 60, p. 227-237), and Pritchard et al. (*Genetics*, 2000, Vol. 155, p.945-959).

Parra, Ott, and Halushka make obvious a method for inferring ancestral proportions and admixture, as applied to claims 1, 84-86, 90, 92-97, 100, 104, and 105 as set forth above.

Parra, Ott, and Halushka do not specifically teach BGA for an Asian ancestral group, as in claims 98-99, and 107-109, four group comparisons, as in claim 101, or the graphical representation as in claims 102 and 103, or generating an ancestral map, as in claim 106.

Kanetsky discloses SNP markers for coding and non-coding regions in white, African, Spanish, Hispanic, Native Indian, Aboriginal, and Asian populations for investigating ancestral relationships of hair and eye color (p. 772, Col. 2, ¶3), as in claims 98, 99, and 101, and 107-109.

Pritchard et al. present several different techniques for inferring proportional ancestry of different ancestral groups. In particular, Pritchard teaches the following: maximum likelihood methods for inferring population structure and calculation of likelihood test statistics wherein alleles may have different effects in different subpopulations [p.230, Col. 2], as in claims 98-99 and 101, and means for graphically displaying ancestral results in triangular format [Fig. 1], as in claims 102 and 103. The computer-based program STRUCTURE is used to estimate population structure for 20 data sets of 50, 200, and 1000 biallelic markers [p. 232, Results], therefore it

would be well within the capabilities of one of ordinary skill in the art to use this program for calculation of a variety of population structures using SNP markers.

Pritchard discloses statistical methods for determining the population structure and admixture (abstract), and specifically discloses an ancestral map and the correspondence to the proportional ancestry (fig. 3 and fig. 6), as in claim 106.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of Parra, Ott, and Halushka to use SNP markers for additional ancestral groups including Asian, as taught by Kanetsky, and generating ancestral maps and displaying results in a easy to read graphical format that indicates populations of origin, as taught by Pritchard, resulting in the practice of the instantly claimed invention with predictable results. One of ordinary skill in the art would have been motivated to combine the above teachings in order to improve ancestral prediction by reducing the number of genetic data used, as provided by Ott, and to estimate the relationship of individual admixture to disease status (e.g. hypertension), as provided by Halushka, or other non-disease characteristics, as provided by Kanetsky et al.

Claims 1, 83-91, 95-99, and 107-110 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shriver et al. (Am. J. Hum. Genet., 1997, Vol. 60, p.957-964), in view of Daly et al. (Nature Genetics, 2001, Vol. 29, p.229-232) and Kruglyak (Nature Genetics, 1997, Vol. 17, p.21-24).

Shriver et al. teach a method for identifying a set of population-specific genetic markers that enable robust estimation of ethnicities for use in forensic settings [p.962, Discussion]. In particular, Shriver et al. teach the following aspects of the instantly claimed invention: searching

the literature (i.e. databases) for markers that would be useful in estimating ancestry of U.S. residents comprising Africans, Europeans, African-Americans, American Indians, European Americans, and Hispanics [p.959, Results]; the identification of six PCR-based genetic markers (i.e. a first population) that are typed in ethnically defined populations with allele frequency differentials (i.e. delta values) > 0.4 (or 40 %) between populations [p.959, Results, Col. 2] and [p.957, Col. 2], as in claim 1, steps a) and b). Methods for calculating the EAE log-likelihood ratio between any two populations [p.958, Methods] and displaying results [Tables 1 and 2]. Selection of a subset of markers (i.e. second population) from those listed in Table 1 and 2 based on the above differential allele frequencies that provides the highest statistical power for ethnic-affiliation estimation (EAE) [p.961, Col. 1, ¶3], as in claim 1, step c); and determining frequency distributions of top markers amongst non-parental populations [Fig. 2A, 2B], wherein loci are genotyped using PCR primers and conditions obtained from the Genome Database (i.e. contacting a sample) [p.961, Col. 1, ¶3], as in claim 1, steps d) and e). Figure 1 presents frequencies of six markers in five intercontinental and intracontinental populations comprising parental (e.g. African) and non-parental groups (e.g. African-American). Identification of population structure based on likelihood distributions used to infer proportional ancestry of mixed (i.e. non-parental) populations [Fig. 3 and 4], as in claim 1, step f). Shriver et al. additionally teach minimizing the effects that linkage disequilibrium has on the computation of likelihood ratios [p.961, Col. 1, ¶3], as in claim 91, and that similar sets of markers for the identification of other members of the population, including Asian [p.963, Col. 1, ¶3], as in claim 98. Therefore, Shriver et al. teaches all aspects of claims 1, 83, 85, 84, 85, 86, 90, 91, 95, 96, 97, and 98.

Shriver et al. do not specifically teach the use of SNP markers or the selection of a second group of SNPs with minor allele frequencies > 1%, as in claims 1, 87-89 and 107-110,

but do teach selection criteria based on frequency differentials and minimizing the effects that linkage disequilibrium would have on the computation of likelihood ratios [p.961, Col. 1, ¶3], which is suggestive of the use SNPs with minor allele frequencies.

Kruglyak beneficially teaches the use of SNPs as biallelic markers over microsatellite markers to provide rapid highly automated genotyping for linkage studies [p.21, Col. 1], as well as assays with high-density microarrays. Kruglyak also suggest parallel screening of SNPs for direct association with disease [p.23, Discussion] and provides guidance on differences between SNPs and microsatellites [p.22]. Therefore, it would be well within the capabilities of one of ordinary skill in the art to practice the method of Shriver using SNPs.

Daly et al. teach a method for selecting a subset of 103 rare SNP markers with minor allele frequency of >5% from a Canadian population (predominantly of European descent) to provide an improved resolution picture of genetic variation and transmission of Crohn's disease linkage disequilibrium analysis [p.229], as in claims 1, 87-89 and 107-110. The method includes the use of maximization likelihood estimates [p.232, Col. 2].

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of Shriver et al. using SNPs as biallelic markers, as taught by Kruglyak, and a second population of SNPs with minor-allele frequencies > 1%, as taught by Daly et al., where the motivation would have been to use markers conducive to automation that provide improved estimation of the relationship of individual admixture to Crohn's disease, in view of Daly et al., resulting in the practice of the instantly claimed invention with predictable results.

CONCLUSION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pablo Whaley whose telephone number is (571)272-4425. The examiner can normally be reached on 9:30am - 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached at 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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